First total synthesis of a new pyrrolizidine alkaloid, amphorogynine A

Hidemi Yoda,* Takahisa Egawa and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering, Shizuoka University, Johoku 3-5-1, Hamamatsu 432-8561, Japan

Received 21 November 2002; revised 19 December 2002; accepted 20 December 2002

Abstract—An efficient and stereodefined strategy is described for the first asymmetric synthesis of a new type of pyrrolizidine alkaloids, amphorogynine A and its 1-epi-isomer. The key 2,4-disubstituted pyrrolidine ring was constructed by elaboration of the chiral lactam derivative incorporating the D-malic acid-derived skeleton through asymmetric cis-allylation of the functionalized allylsilane. © 2003 Elsevier Science Ltd. All rights reserved.

Amphorogynine A together with structurally related compounds, amphorogynines B, C, and D, was first isolated in 1998 by Pais and co-workers from the leaves of Amphorogyn spicata Stauffer and Hürlimann (Santalaceae) in a research for alkaloids in New Caledonian plants.1 After structural characterization by the same group based on spectroscopic methods using chemical correlations, these were revealed to be a new class of pyrrolizidine alkaloids possessing a 1,6-disubstituted structure (Fig. 1).1 These alkaloids differ from the position of the substituents on the pyrrolizidine ring. Whereas amphorogynines possess a hydroxyl group at the C(6) position, the well known necines generally bear this substituent at the C(7) position of the pyrrolizidine.2 Since such alkaloids showing substituted functions at both C(1) and C(6) only have not been reported previously,3 their structural and stereochemical complexity coupled with their diverse and potentially useful characteristics would make them hereafter inviting targets for synthesis. The synthesis of this type of compounds poses interesting and often unsolved problems of sterecontrol. Consequently, no report concerning the total synthesis of 1 along with related natural products has appeared to date.

With these considerations in mind, we wish to communicate the details of the first asymmetric synthesis of 1 and its 1-epimer (6-epi-amphorogynine B) by means of requisite stereoselective allylation of the α-hydroxypyrrolidine intermediate elaborated from D-malic acid.

As shown in Scheme 1, N-MPM(p-methoxybenzyl)imide 6 obtained from D-malic acid (5) was reduced regioselectively with NaBH₄ and readily effected by BF₃·OEt₂-induced reductive deoxygenation with Et₃SiH to afford the acetoxylactam intermediate. After

![Figure 1](image-url)

**Keywords:** amphorogynine; pyrrolizidine alkaloid; allylation; lactam; malic acid.

* Corresponding author. Tel.: +81 53 478 1150; fax: +81 53 478 1150; e-mail: tchyoda@ipc.shizuoka.ac.jp

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.

PH: S0040-4039(03)00070-4
Scheme 1. Reagents and conditions: (a) 1. NaBH₄, MeOH, 0°C; 2. BF₃·OEt₂, Et₂SiH, CH₂Cl₂, 0°C; 69% (two steps); 3. K₂CO₃, MeOH; 97%; 4. BnBr, Ag₂O, DME; 92%; (b) 1. CAN, CH₂CN·H₂O (9:1); 93%; 2. (Boc)₂O, DMAP, Et₃N, CH₂Cl₂, 0°C; quant.; 3. Pd (black), 4.4% HCOOH·MeOH, 45°C; quant.; 4. TBDDPSi, imidazole, CH₂Cl₂; 94%; (c) 1. NaBH₄, MeOH, 0°C; 2. CH₂=CHCH₂SiMe₃, BF₃·OEt₂, CH₂Cl₂, −78°C; 72%; (9a) (two steps); MPOMO(CH₂)₂CH·CHCH₂SiMe₃, BF₃·OEt₂, CH₂Cl₂, −78°C; 47%; (9b) (two steps); (d) 1. DDQ, CH₂Cl₂·H₂O (11:1), 0°C; 90%; 2. CBr₄, PPh₃, CH₂Cl₂; 96%; (e) 1. OsO₄, NMO, acetone·H₂O, 0°C; 2. NaOEt, ether·THF·H₂O (1:1:2); 88% (two steps); 3. Bz₂Na, MeOH·H₂O (9:1); 89%; (f) 1. Bu₄NF, THF, 0°C; 87%; 2. 3-(p-benzyloxy-m-methoxyphenyl)propanoic acid, EDCI, DMAP, CH₂Cl₂, 0°C; 70%; (g) 1. BF₃·OEt₂, CH₂Cl₂; −15°C; 2. NaHCO₃, H₂O; 85% (two steps); 4. H₂, Pd/C, CH₃COOEt; 58% (amphorogynine A (1)); 26% (1-epi-amphorogynine A (6-epi-amphorogynine B)) (14).

In summary this work constitutes the first synthesis of the natural pyrrolizidine alkaloid, amphorogynine A, and the key to the correct construction of a pyrrolizidine ring system, 9b was in turn submitted to deprotection of the MPM moiety followed by introduction of the bromo function as the leaving group. The olefinic part in the pyrrolidine derivative 10 thus obtained was then cleaved via dihydroxylation to give the aldehyde intermediate, which was successively subjected to bromine-induced oxidation, leading to the corresponding methyl ester 11 in 89% yield. The remaining side unit in amphorogynines prepared from vanillin was then introduced in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and DMAP) after desilylation. Finally, the coupling product 12 was effected by deprotection with BF₃·OEt₂, together with concomitant cyclization, followed by debenzylation of the resulting pyrrolizidine 13 with 5% Pd on carbon to produce the desired compound, amphorogynine A (1), accompanying with its 1-epimer (6-epi-amphorogynine B) 14. These were readily separated by column chromatography on silica gel and demonstrated that the less mobile compound (CHCl₃·MeOH = 3:1; TLC R₄ 0.55) corresponded to the natural product 1 (58%), [α]D +52.1° (c 0.57, CHCl₃) (lit. [α]D +53° (c 1, CHCl₃) 1), and the more mobile substance (CHCl₃·MeOH = 3:1; TLC R₄ 0.60) was the 1-epi-isomer 14 of amphorogynine A (6-epi-amphorogynine B) (26%), [α]D +15.7° (c 0.38, CHCl₃), based on their spectral data, respectively. The spectral data of synthetic (+)-1 were completely identical to those of the reported natural product.

In summary this work constitutes the first synthesis of the natural pyrrolizidine alkaloid, amphorogynine A,
and verifies the structure proposed in the literature for this natural product, since no report concerning the total synthesis of amphorogynines has appeared to date.

Acknowledgements

This work was supported in part by a Grant-in-Aid (No. 13640530) for Scientific Research from Japan Society for the Promotion of Science.

References

3. Hartmann, T.; Witte, L. In Alkaloids Chemical and Biological Perspectives; Pelletier, W. S., Ed.; Elsevier: Amsterdam, 1995; Vol. 9, p. 155.
7. The absolute stereochemistry of the newly created carbon center in 9a was unambiguously proved to be S after derivatisation of 9a to the benzyl ether by comparing its spectral data with those of the trans-N-Boc-pyrrolidine 19, which was in turn elaborated from d-tartaric acid-derived C2-imi di 15 employing cis-selective allylation reaction8 as shown in Scheme 2.
11. Cis-stereochernistry in the pyrrolidine ring of 9b was determined based on its spectral data of synthetic (+)-1.
12. To begin with, experiments have been performed on a dihydroxylation reaction mediated by OsO4 employing the tosylated compound 20 as shown below. The reaction, however, resulted in the preparation of the corresponding simultaneously cyclized products of 21 and 22 as an inseparable mixture.


16. 1H and 13C NMR data (CDCl3) for 14. 1H NMR δ 1.71–2.36 (4H, m), 2.37–2.96 (7H, m), 2.98–3.44 (2H, m), 3.57–3.94 (1H, m), 3.84 (3H, s), 3.89 (3H, s), 4.98–5.63 (1H, m), 5.98 (1H, br), 6.62 (1H, d, J=8 Hz), 6.66 (1H, s), 6.79 (1H, d, J=8 Hz). 13C NMR δ 30.5, 30.8, 36.1, 37.6, 49.9, 51.8, 54.2, 55.7, 59.7, 66.6, 76.5, 111.1, 114.7, 120.6, 131.9, 144.3, 146.8, 172.6, 173.9.
学霸图书馆

www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具